AF/1648

CASE D0017NP

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Keith R. Lange		October 14, 2004
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE APPLICATION OF

BLAIR ET AL.

APPLICATION NO: 09/876,680

FILED: JUNE 7, 2001

FOR: HIV-1 REPORTER VIRUSES AND THEIR USE IN ASSAYING ANTI-VIRAL COMPOUNDS

Examiner: Myron G. Hill

Group Art Unit: 1648

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APPEAL BRIEF PURSUANT TO 37 CFR §1.192

Sir:

This is an appeal to the Board of Appeals from a decision mailed November 28, 2003, in which the Examiner finally rejected Claims 1-23 of the above-identified application. Applicant has timely filed a Notice of Appeal by certification on May 14, 2004. This brief is being filed pursuant to that Notice of Appeal.

The filing date of the Notice of Appeal is May 14, 2004. Therefore, this brief is due July 14, 2004 under 37 C.F.R. §1.192(a). A Three Month Extension of Time is being filed herewith

under 37 C.F.R. §1.136(a), thereby extending the due date for filing this brief until October 14, 2004. Therefore, this brief is deemed to be timely filed.

Kindly charge $1320.00 to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company. This amount reflects the filing fee set forth in 37 C.F.R. §1.17(c) and the fee for a Three Month Extension of Time under 37 C.F.R. §1.17(a)(3). As required by 37 CFR §1.192, this brief is being filed in triplicate. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

1. REAL PARTY IN INTEREST

Applicants Wade Blair and Timothy P. Spicer filed this application on June 7, 2001. The real party in interest in the present appeal is Bristol-Myers Squibb Company, having acquired rights from the aforementioned Applicants by way of a Assignments recorded on August 16, 2002 at Reel 012993, Frame 0830.

2. RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are known to appellants or appellants' legal representative which will directly affect or be directly affected by or have bearing on the Board's decision in this appeal.

3. STATUS OF CLAIMS

Claims 1-23 are presently pending in the application. Claims 1-4, 10, 11, 13-15, 21 and 22 stand rejected under 35 U.S.C. §03(a) as allegedly being unpatentable over Haseltine and Liu et al.

Claims 5, 6, 16 and 17 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Haseltine and Liu et al., as applied to Claims 1-4, 10, 11, 13-15, 21 and 22 and Gibbs.

Claims 9-12 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Haseltine and Liu et al., as applied to Claims 1-4, 10, 11, 13-15, 21 and 22 and Shi et al.

Claims 7, 8, 18-20 and 23 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Haseltine and Liu et al., as applied to Claims 1-4, 10, 11, 13-15, 21 and 22 and Collman or Li or Shi.

The rejections of Claims 1-23 are being appealed.

4. STATUS OF AMENDMENTS

A First Office Action was issued in this case on January 23, 2003. In response thereto, Applicants filed a Response on June 23, 2003. In response thereto, the Examiner issued a Final Office Action dated November 28, 2003 finally rejecting Claims 1-23.

In the Final Office Action, the Examiner withdrew the outstanding rejections under 35 U.S.C. §102 and presented modified grounds of rejection under 35 U.S.C. §103(a). The present appeal is taken from the Final Office Action.

5. SUMMARY OF INVENTION

The claimed invention is directed to a replication-competent HIV-1 reporter virus that allows rapid high volume screening of anti-viral compounds. The reporter virus encodes a reporter gene introduced in place of a viral gene not essential for replication culture that serves as a marker for viral replication and can be analyzed in a simple and rapid manner. Thus, the present invention allows for the establishment of high throughput screens for anti-viral compounds that include all viral targets required for replication in culture.

6. ISSUE

The issue on appeal is:

Is the claimed invention obvious under 35 U.S.C. §103(a) in view of Haseltine and Liu?

7. GROUPING OF CLAIMS

The claims stand or fall together for the contested grounds of rejection for the sole purpose of allowing the Board to select a single claim for review, and to decide the appeal as to the grounds of rejection on the basis of that claim alone.

8. ARGUMENT

A. CLAIMS 1-4, 10, 11, 13-15, 21 AND 22 ARE NOT OBVIOUS UNDER 35 U.S.C. §103(a) IN VIEW OF HASELTINE AND LIU.

In the outstanding rejection under 35 U.S.C. §103(a), the Examiner states that Claims 1-4, 10, 11, 13-15, 21 and 22 are unpatentable over Haseltine and Liu. The Examiner alleges that one of ordinary skill in the art at the time of the invention would have been familiar with doing a "CAT" assay and Haseltine teaches that a reporter gene is needed. The Examiner alleges that Liu teaches that secreted reporter proteins offer the advantage of permitting monitoring over time and light-emitting reporter gene assays are particularly convenient because their assays offer great sensitivity and permit easy quantitation of the reporter gene (11/28/03 Office Action, p. 4). The Examiner therefore alleges that one of ordinary skill in the art at the time of the invention would know that high throughput assays require steps that can be automated or carried out with large numbers of samples.

The Examiner further states that Grentzmann teaches that renilla luciferase is suitable for high throughput assays, and therefore alleges that one of skill in the art would have been motivated to replace the CAT reporter gene of Haseltine with a secreted reporter gene as taught by Liu because the infected cells could be monitored over time, the ease of quantitation of reporter gene, and higher level of sensitivity that is possible with the reporter genes of Liu as compared to the CAT reporter gene of Haseltine. For the reasons stated herein, Applicants disagree and respectfully request that the Board reverse the decision of the Examiner.

In making the present rejections under Section 103, the Examiner has merely presented several references without providing the requisite teaching, suggestion or motivation to support a rejection under Section 103. The Examiner is merely using *ex post facto* reasoning to allege that

the present invention is unpatentable, without providing the requisite showings to support even a *prima facie* case of obviousness.

As discussed in the Background of the Invention section of the present specification (pages 2-3), single-cycle infectious HIV-1 reporter viruses encoding luciferase as the reporter gene have been described, but steps post-HIV gene expression in an infected cell, such as HIV protease mediated processing of viral precursor polypeptides required for virion maturation, are not easily measured using such reporter viruses. Thus, such viruses are not useful for testing for possible late stage replication inhibitors. Also, replication-competent HIV-1 reporter viruses are known, but are not useful for high volume anti-viral assays because the reporter gene products they encode, such as CAT, cannot be measured by simple and rapid assays. Haseltine discloses an example of such a virus.

The Examiner fails to set forth any motivation to use a reporter of Liu in the virus of Haseltine. As discussed in the present specification, the virus of Haseltine is not suitable for use in a high throughput screening assay due, for example, to the limitations of the reporter used. Haseltine does not suggest any manner of remedying these problems and provides no teaching as to how one skilled in the art would modify the HIV-1 virus of Haseltine to arrive at the present invention. Further, the Examiner has not provided a specific reference in Haseltine showing where such a teaching is provided. Merely pointing out that a particular reporter used in the present invention was known in the art, as the Examiner has done by citing Lui, clearly cannot remedy this deficiency.

Moreover, Applicants point out that previous attempts to modify HIV-1 proviral clones with a reporter gene, such as that of Lui, failed to produce replication competent reporter viruses. For example, as set forth in the present specification, the JRFNFLuc virus, which encodes a firefly luciferase gene, was constructed in a manner similar to that set forth known in the art (Chen et al., J. Virol. (1994) 68:654-660). As set forth at page 17 of the present specification, this virus failed to produce firefly luciferase after the third day of infection, indicating that mature virus core particles were not made and that the virus was not replication competent.

Accordingly, at the time of the present invention, the art failed to teach or suggest the replication competent reporter viruses of the present invention which are useful in high throughput assays.

As neither Haseltine nor any other reference provides the requisite teaching to solve the problems which existed in the art at the time of the present invention, Applicants respectfully request that the Board reverse the outstanding rejection under Section 103.

B. CLAIMS 5, 6, 16 and 17 ARE NOT OBVIOUS UNDER 35 U.S.C. §103(a) IN VIEW OF HASELTINE AND LIU AS APPLIED TO CLAIMS 1-4, 10, 11, 13-15, 21 AND 22 AND GIBBS.

The Examiner has maintained the rejection of Claims 5, 6, 16 and 17 under 35 U.S.C. 103(a) as being unpatentable over Haseltine and Liu, as applied to claims 1-4, 10, 11, 13-15, 21 and 22 and Gibbs. The Examiner alleges that Haseltine teaches a replication competent HIV-1 virus with a non-essential region of the virus replaced and a heterologous DNA inserted as a reporter gene to trace HIV infection or monitor the effects of anti-HIV drugs in a screening assay. The Examiner acknowledges that Haseltine does not teach clone pNL4-3 or deletion of some or all vpr, but states that Gibbs teaches proviral clone pN4-3 and that vpr is a non-essential region.

For the reasons set forth above, Applicants respectfully submit that Haseltine merely sets forth known replication-competent HIV-1 reporter viruses which are not suitable for use in a high throughput screening assay. As such, Gibbs, which discloses proviral clone pN4-3 and that vpr is a non-essential region, cannot remedy the deficiencies of Haseltine.

C. CLAIMS 9-12 ARE NOT OBVIOUS UNDER 35 U.S.C. §103(a) IN VIEW OF HASELTINE AND LIU AS APPLIED TO CLAIMS 1-4, 10, 11, 13-15, 21 AND 22 AND SHI.

The Examiner has maintained the rejections of Claims 9-12 under 35 U.S.C. 103(a) as being unpatentable over Haseltine and Liu, as applied to claims 1-4, 10, 11, 13-15, 21 and 22 and Shi. Applicants respectfully point out that Shi merely discloses the proviral clone HIV-1-Lai and uses MT-2 to grow the virus. For the reasons set forth above, Applicants respectfully submit that

Haseltine merely sets forth known replication-competent HIV-1 reporter viruses which are not suitable for use in a high throughput screening assay. As such, Shi, which merely discloses the proviral clone HIV-1-Lai and uses MT-2 to grow the virus, cannot remedy the deficiencies of Haseltine.

D. CLAIMS 7, 8, 18-20 and 23 ARE NOT OBVIOUS UNDER 35 U.S.C. §103(a) IN VIEW OF HASELTINE AND LIU AS APPLIED TO CLAIMS 1-4, 10, 11, 13-15, 21 AND 22 AND COLLMAN OR LI OR SHI.

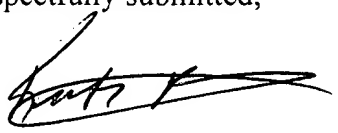
The Examiner has rejected claims 7, 8, 18-20 and 23 under 35 U.S.C. §103(a) as being unpatentable over Haseltine and Liu, as applied to claims 1-4, 10, 11, 13-15, 21 and 22 and Collmann or Li or Shi. The Examiner alleges that Haseltine teaches a replication competent HIV-1 virus with a non-essential region of the virus replaced and a heterologous DNA inserted as a reporter gene to trace HIV infection or monitor the effects of anti-HIV drugs in a screening assay. The Examiner acknowledges that Haseltine does not teach proviral clone of pYU-2, but states that Collman teaches an infection clone of HIV-1, p89.6 which has a novel tropism, Li , teaches an infectious proviral clone of pYU-2 and Shi teaches the proviral clone of HIV-Lai and the use of MT-2 cells to grow virus. The Examiner alleges that one skilled in the art would know that the provirus of Collman or Li or Shi could be used in the place of Haseltine.

For the reasons set forth above, Applicants respectfully submit that Haseltine merely sets forth known replication-competent HIV-1 reporter viruses which are not suitable for use in a high throughput screening assay. As such, none of Collman, Li or Shi, each of which discloses a various provirus, can remedy the deficiencies of Haseltine.

CONCLUSION

For the reasons set forth above, Applicants respectfully submit that the claimed invention is not obvious under 35 U.S.C. §103(a). Accordingly, the Board is respectfully requested to reverse the appealed decisions of the Examiner.

Respectfully submitted,



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Dated: October 14, 2004

9. APPENDIX

Appealed Claims

1. A vector that encodes a replication competent HIV-1 virus, said vector comprising an HIV-1 genome in which a region non-essential for viral replication has been replaced by a reporter gene, wherein said vector is suitable for use in a high volume anti-viral assay.

2. The vector according to claim 1, wherein said reporter gene is selected from the group consisting of the renilla luciferase reporter gene, the SEAP reporter gene[, the CAT gene,] and the green fluorescence protein gene.

3. The vector according to claim 2 wherein said reporter gene is selected from the group consisting of the renilla luciferase reporter gene and the SEAP reporter gene.

4. The vector according to claims 1, 2 or 3 wherein the region non-essential for viral replication encodes the nef gene or a fragment of the nef gene.

5. The vector according to claims 1, 2 or 3 wherein the region non-essential for viral replication encodes the vpr gene or a fragment of the vpr gene.

6. The vector according to claims 1, 2 or 3 wherein the HIV-1 genome is the genome of the pNL4-3 proviral clone.

7. The vector according to claims 1, 2 or 3 wherein the HIV-1 genome is the genome of the pYU-2 proviral clone.

8. The vector according to claims 1, 2 or 3 wherein the HIV-1 genome is the genome of the p89.6 proviral clone.

9. The vector according to claims 1, 2 or 3 wherein the HIV-1 genome is the genome of the HIV-1 Lai proviral clone.

10. A cell comprising the vector of claim 1, 2 or 3.

11. A method of screening for compounds that exhibit anti-viral activity against HIV-1 comprising:

a) adding a test compound to mammalian cells infected or cells to be infected with the vector according to claim 1, 2 or 3; and

b) comparing reporter gene activity in cells exposed to the test compound to the level of expression in control cells,

wherein a reduction in the level of reporter gene expression indicates the test compound inhibits HIV-1 replication.

12. The method according to claim 8, wherein the mammalian cells are MT-2 #18 cells.

13. A vector that encodes a replication competent HIV-1 virus, said vector comprising an HIV-1 genome in which a region non-essential for viral replication has been replaced by a nucleic acid sequence encoding a functional renilla luciferase enzyme, wherein said vector is suitable for use in a high volume anti-viral assay.

14. The vector according to claim 13 wherein the renilla luciferase gene contains a cysteine to alanine substitution that results in a functional renilla luciferase enzyme.

15. The vector according to claim 13 wherein the region non-essential for viral replication encodes the nef gene or a fragment of the nef gene.

16. The vector according to claim 13 wherein the region non-essential for viral replication encodes the vpr gene or a fragment of the vpr gene.

17. The vector according to claim 13 wherein the HIV-1 genome is the genome of the pNL4-3 proviral clone.

18. The vector according to claim 13 wherein the HIV-1 genome is the genome of the pYU-2 proviral clone.

19. The vector according to claim 13 wherein the HIV-1 genome is the genome of the p89.6 proviral clone.

20. The vector according to claim 13 wherein the HIV-1 genome is the genome of the HIV-1 Lai proviral clone.

21. A cell comprising the vector of claim 13.

22. A method of screening for compounds that exhibit anti-viral activity against HIV-1

comprising:

a) adding a test compound to mammalian cells infected or cells that will be infected with the vector according to claim 13; and

b) comparing reporter gene activity in cells exposed to the test compound to the level of expression in control cells,

wherein a reduction in the level of reporter gene expression indicates the test compound inhibits HIV-1 replication.

23. The method according to claim 13, wherein the mammalian cells are MT-2 #18 cells.